The PIA2 variant of the platelet glycoprotein IIIa as a genetic risk factor for IVF implantation failure: accumulating evidence

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Received: 21 April 2016 / Accepted: 25 April 2016 / Published online: 30 April 2016
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We read with great interest the recent article of Patounakis et al. [1] who examined the potential role of nine genetic thrombophilic factors in in vitro fertilization (IVF) outcome. Even though the authors came to the conclusion that the thrombophilic single nucleotide polymorphisms (SNPs) which were evaluated, individually or cumulatively, do not have any significant effect, an important clinical finding, the correlation of the genetic polymorphism PIA1/PIA2 (T1565C-Leu33Pro) (rs5918) of the platelet glycoprotein IIIa (GpIIIa) gene with implantation failure after IVF embryo-transfer (IVF-ET failure), was overlooked.

Expanding the findings of many studies concerning miscarriages, a number of researchers reported that thrombophilic factors affect the success of implantation or the accomplishment of clinical pregnancy in IVF treatment. A large majority of these studies examined the role of anti-phospholipid antibodies in the IVF outcome, and Di Nisio et al. [2] in their meta-analysis of 20 case-control studies including 3542 patients calculated a 3.3-fold increased risk, although this was not confirmed in the respective analysis of cohort studies. On the contrary, since the first published study by Grandone et al. [3] which found that the prevalence of the factor V Leiden (FVL) and prothrombin 20210A allele carriers cumulatively was significantly higher in a small

group of 18 women with ≥ 3 IVF-ET failures (implantation failures or fetal loss), as compared with 216 fertile women with uneventful pregnancies after spontaneous conception, a small number of relative studies that followed have not given conclusive results while certain correlations of genetic thrombophilic factors with IVF-ET failure have ensued with an additive non-special approach. Moreover, from the genetic variants that are relative to the coagulation factor gain of function (factors I, II, V, XII), anticoagulant deficiency (plasminogen activator inhibitor-1, PAI-1) or hyperhomocysteinemia (methylene tetrahydrofolate reductase, MTHFR) which were assessed in the study of Patounakis et al., only FVL [4, 5] and MTHFR-677TT [4, 5] and MTHFR-1298CC [6] homozygosities have been singly associated with a negative IVF outcome so far, while non-correlation was also found in the meta-analysis of Di Nisio et al. with the exception of FVL [2].

We consider that the most significant finding of the study of Patounakis et al. is the indication of additional suggestive evidence (although non-significant under strict statistical consideration) that the presence of the GpIIIa-PIA2 allele increases the risk of IVF-ET failure. Clinical pregnancy rate was approximately 17 % higher for the GpIIIa-PIA1 homozygotes than that in the GpIIIa-PIA2 carriers (56 versus 48 %, $p=0.010$). This correlation probably has not been able to reach strict statistical significance due to the use of an unselected group of participants undergoing their first IVF cycle, despite their large number, and the simultaneous comparison of nine SNPs which decreased the power of the study due to the necessary Bonferroni correction.

The GpIIIa-PIA2 allele constitutes a significant risk factor for arterial thrombosis [7, 8], and more recent studies show that probably it is positively associated with deep venous thrombosis, as well [9]. In a recent pilot study of 60 strictly selected women with unexplained recurrent IVF-ET failures excluding all cases with other known risk factors, we reported an increased occurrence of carriers of the GpIIIa-PIA2 allele,

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Capsule In contrast to the inconclusive results yielded for most inherited thrombophilic factors, there is accumulating evidence that the PIA2 allele of the platelet glycoprotein IIIa gene is associated with increased risk of IVF implantation failure.

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in comparison with a control group of 60 fertile women with no history of pregnancy or vascular complications, resulting in an odd ratio of 2.9 and a stronger association for the younger participants [10]. Furthermore, in a previous study in Bulgaria, Ivanov et al. [8] also found a 2.6-fold increased risk during the comparison of 67 women with IVF-ET failures with 96 fertile controls [11]. The only study so far that has not concluded in a positive finding regarding the role of Gp111a-PIA2 allele in pathogenicity of IVF-ET failure was a small underpowered study of 42 women with recurrent IVF-ET failure and 20 fertile controls in which no analytical statistical analysis was cited [12].

The suggested plausible mechanism behind the failure of clinical pregnancy achievement after IVF in women with genetic thrombophilic defects, of microthrombosis of initial vascularization, and the impairment of initial perfusion of the embryo seems inadequate to fully interpret the implication of thrombophilia in IVF-ET failure. However, glycoprotein 111a (integrin beta3) participates in the process of the implantation not only involved in platelet aggregation but also as a subunit of integrin alphaVbeta3 which is present in the interactions of endometrial and embryonic cells [11].

Patounakis et al. reported that the Gp111a-PIA2 allele is linked to a higher platelet sensitivity to antiplatelet drugs which however was not concluded by a large relative meta-analysis [13]. Furthermore, in the study of Patounakis et al., a notable number of 253 patients received low-dose aspirin (81 mg). It would be interesting if the authors reported the indication for aspirin use by these women and also if there was a significant difference in clinical pregnancy rates among carriers and non-carriers of the Gp111a-PIA2 allele among aspirin-treated participants.

In conclusion, in contrast to the inconclusive results yielded for most inherited thrombophilic factors, there is accumulating evidence for the involvement of Gp111a-PIA2 allele as a risk factor for IVF-ET failure, the limiting step of IVF therapy, and there is urgent need for further confirmation in larger scale studies. The Gp111a-PIA2 factor especially in synergy with the 807T allele of the glycoprotein 1a gene as we have shown recently [10] underlines the importance of the platelet-associated thrombophilia and could have a remarkable clinical impact on potential medical intervention with an individualized approach of the aspirin therapy to improve unexplained poor IVF implantation outcome [14].

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